Guidelines for Managing Anaemia and Iron Deficiency in the Perioperative Setting

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Summary and Key Recommendations

- Anaemia and allogenic blood transfusion are associated with poor outcomes for surgical patients.
- The WHO definition of anaemia has been criticized recently. Expert opinion favours a Haemoglobin (Hb) of 130g/l or more, in both males and females.
- Patients should be screened for anaemia and iron deficiency at the earliest opportunity in the surgical care pathway.
- Surgical procedures with a moderate to high risk of blood loss >500ml or a transfusion risk of > 10% are deemed the most suitable.
- Anaemia and iron deficiency are easily treated in the preoperative setting. All patients should be offered iron therapy in line with NICE guidance.
- Patients with absolute iron deficiency and >6 weeks from surgery should be given a trial of oral iron. Patients <6 weeks from surgery, identified with Functional Iron deficiency or have a failed oral iron treatment should be offered intravenous iron.
- Strict adherence to preoptimization pathways reduces allogenic transfusion however significant cost benefit realization requires adherence to all of the pillars of Patient Blood Management.
INTRODUCTION

Anaemia affects 2.36 billion people worldwide with the prevalence of iron deficiency estimated to be around 1.46 billion individuals. [1] In the surgical setting, prevalence varies between surgical specialties ranging between 20-45% [2]. The WHO recommends that measures should be taken to optimise patients’ own blood volume using a patient blood management (PBM) approach [3]. Optimisation of anaemia status is the first pillar in this proposal and supported by a wealth of guidance from international expert groups including the National Institute of Clinical Excellence (NICE) [4,5], the Association of Anaesthetists of Great Britain and Ireland [6] and The Society for Advancement of Blood Management [7].

More recently, the international consensus statement on the perioperative management of anaemia and iron deficiency challenges how we have previously defined anaemia in the preoperative setting [8]. Munoz et al. suggest that the preoperative haemoglobin should be ≥ 130 g/l in both men and women based upon 2 large studies where outcomes in women worsened when the preoperative haemoglobin was below 130 g/l [9,10]. The following guidelines pull together these opinions and available evidence.

Why is optimising anaemia important in the perioperative setting?

Patients presenting with anaemia at the time of surgery show increased postoperative morbidity and mortality [11,12]. Mussallam et al. analysed data from 211 hospitals and over 200,000 patients in the American College of Surgeons National Surgical Quality Improvement Programme, looking at the prevalence and outcomes of patients across a range of surgical disciplines. An increased risk of 30 day mortality and morbidity was demonstrated in patients who were anaemic compared to those that were not anaemic on the day of surgery [9]. Klein et al. showed similar results in cardiac surgery and also showed that women were at higher risk. It is difficult to separate the cause and effect of anaemia over the effect of an increased requirement for allogenic blood transfusion that leads to poorer outcome [10]. Evidence of poorer outcome in patients that require a blood transfusion during their surgery for cancer is compelling, blood transfusion being an independent risk factor for survival and tumour recurrence [13,14]. The updated Cochrane review by Preston et al. in 2012 supports this conclusion and moreover there was no evidence of benefit in preoperative transfusion [15].

Clearly, maintaining freedom from transfusion is more likely if the patient presents in a non-anaemic state. Implementation of the 3 pillars of PBM [16] improve patient outcome, reduces health care costs and saves blood [17]. Making provision to implement PBM could not be more timely in light of the COVID 19 pandemic, where the donor pool has reduced and supply may outstrip demand as the NHS returns to full operative capacity [18,19]. All 3 pillars should be implemented to optimise haemoglobin in the perioperative setting.

What is the cause of anaemia in the surgical patient?

Iron deficiency is the commonest cause of anaemia in the surgical population. Chronic kidney disease and nutrients such as B12 and folate deficiency are less common causes [20,21]. The origin of iron deficiency is complex. Absolute iron deficiency exists when iron stores are severely depleted eg. chronic ongoing blood loss from menstruation, a tumour, or chronic non-steroidal anti-inflammatory use. Functional iron deficiency is the inability to mobilise iron from stores. Patients may have normal or elevated iron stores in this state. The inflammatory process, chronic in the preoperative state and acute in the postoperative state lead to upregulation of the hormone
hepcidin [22]. This hormone is regulated by interleukin 6. Increased hepcidin downregulates the ferroportin receptor in the gastrointestinal tract preventing iron uptake from the diet or iron supplements. It is important to understand the mechanism of iron deficiency in order to treat the patient appropriately. Preoperative pathways should reflect these differences.

What is the definition of anaemia and iron deficiency, who needs investigation?

All patients presenting for surgery with a moderate to high blood loss (>500ml) OR a transfusion risk of >10% should be investigated for anaemia and iron status [2,8]. The WHO continue to define anaemia as Hb <130g/l in men and <120g/l in women whereas Blaudszun et al. consider that the haemoglobin threshold should be identical for both sexes. Women have a lower circulating blood volume, lower body surface area and are more likely to require allogenic blood transfusion and this is supported by data on women with haemoglobin 120-129 g/l requiring more transfusions. It is now more widely accepted that the haemoglobin threshold prior to surgery should be 130g/l in both sexes [23].

The definition of absolute iron deficiency is a serum Ferritin < 30mcg/l. Ferritin > 30mcg/l and Transferrin saturation <20% and/ or elevated CRP are suggestive of functional iron deficiency. If these tests are normal in the presence of anaemia, B12, folate and serum creatinine should be evaluated. This is demonstrated in an ideal pathway by Munting et al [2], and we have adapted this for our Pre-optimisation and assessment clinic locally. (See Figure 1)

Timing of investigation and treatment

Preoperative testing for anaemia and iron deficiency should be done as early as possible in the patient pathway. Ideally this should be done in the primary care setting but this is rarely achieved. Services differ between surgical specialties and hospitals but as a routine the patient should be tested at the point of diagnosis or ‘listing’ for surgery. Pre-assessment is generally too late in the patient pathway. Minimum tests should include a full blood count (FBC), anaemia screen (to include ferritin, B12 and folate if indicated) and CRP. It is important to remember that patients identified with absolute iron deficiency in a non-urgent surgical specialty should be sent via their GP for urgent endoscopy.

Timing of surgery is important. If time to surgery is more than 6 weeks, patients should be given a trial of oral iron as per NICE recommendations. All patients should have a repeat FBC and offered intravenous iron if the haemoglobin response has been inadequate or the patient has had significant side effects [5]. Oral iron is ineffective in the postoperative setting secondary to acute inflammation, emphasizing the need to investigate and treat in the preoperative period.

Oral iron - recommendations for dosing

There are many preparations of oral iron. The recommended daily dose is 40-60mg of elemental iron per day which varies between brands [8]. The table below represents the iron content of the commonly used iron tablets and the elemental iron content per tablet. Tablets can be given at a higher dose on an alternate day basis. However, we have found that patients forget which day they have taken the tablet and then avoid taking the iron, leading to treatment failure. Monitoring for efficacy of oral iron is essential and should be undertaken 4 weeks following the start of treatment. A longer treatment period with up to 6 months is required to replace iron stores completely.
Side effects of oral iron are frequent, between 30-70% in one systematic review [24], with patients describing constipation, change of bowel habit, loss of appetite, abdominal pain and dyspepsia.

<table>
<thead>
<tr>
<th>IRON PREPARATION</th>
<th>AMOUNT</th>
<th>ELEMENTAL IRON CONTENT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ferrous Fumarate</td>
<td>200mg</td>
<td>65mg</td>
</tr>
<tr>
<td>Ferrous Gluconate</td>
<td>300mg</td>
<td>35mg</td>
</tr>
<tr>
<td>Ferrous Sulphate</td>
<td>300mg</td>
<td>60mg</td>
</tr>
<tr>
<td>Ferrous Sulphate, dried</td>
<td>200mg</td>
<td>65mg</td>
</tr>
</tbody>
</table>

Intravenous Iron - recommendations, when to use

NICE guidance (NG 24) recommends intravenous iron should be started in the following circumstances:

- Short time to surgical intervention <6 weeks
- Poor tolerance to oral iron
- Oral iron ineffective at 4 weeks
- Functional Iron deficiency

Intravenous iron is a safe treatment. Safety data from a review of over 19,000 patients by Avni et al demonstrated that there was no increase in serious adverse events [25]. Infection was identified as a possible association but this was with a rarely used iron preparation (Ferrous Gluconate). Anaphylaxis is a possible complication of intravenous iron preparations and needs to be indicated in the drug safety information produced by the pharmaceutical companies. The risk however is extremely small [25,26].

With this in mind, intravenous iron should be delivered in a setting where patients can be monitored for blood pressure, heart rate and oxygen saturation prior to, 15mins and 30 minutes after the infusion. This could be a medical or surgical day case unit, an endoscopy unit or an intravenous drug suite; there are many options. The Cardiff prescription, pre infusion questionnaire and patient monitoring proforma are shown in Figure 2. The newer preparations of iron allow full replacement of iron stores at one sitting and this proforma has the iron dose precalculated to body weight with a simplified questionnaire to identify patients at higher risk of drug reaction.

As for any intravenous drug, a reaction management algorithm should be in place. Nursing teams should be trained to manage minor reactions such as flushing described as a Fishbane reaction, chest tightness and back discomfort. All patients should be given information on the drug before consenting to the procedure.

Erythropoeitin

Ideally, a transferrin saturation (TSAT) <20% should be used to identify patients with functional iron deficiency. Those with a mixed picture or an element of bone marrow failure which is common in the elderly may not have the same response to intravenous iron as those with absolute iron deficiency. These patients may be suitable for treatment with Erythropoietin, but this is dependent
on the surgery type, risk of transfusion and patient risk factors. A separate pathway for these patients should be developed in liaison with local haematologists. This would also be a suitable treatment option for patients who refuse blood for religious beliefs [29].

Postoperative Anaemia

In major surgical interventions anaemia maybe present in up to 90% of patients in the post operative period. This is multifactorial in origin, untreated preoperative anaemia, perioperative blood loss, blunted erythropoiesis secondary to the acute inflammatory response and haemodilution being contributary factors [27]. Monitoring of post-operative haemoglobin is dependant on the severity of blood loss and destination of the patient postoperatively. However, as a minimum, all patients should have a post-op Day 3- 4 FBC.

The nature of postoperative anaemia does not lend itself to oral iron. Intravenous iron is the first choice in patients with significant blood loss or iron deficiency identified in the preoperative setting [28]. Serum Ferritin is a poor marker for iron deficiency post operatively and transferrin saturation should be performed if iron status is unknown. Patients who are symptomatic when they reach the transfusion trigger, usually 75-80g/L, may be considered for a packed red cell transfusion as per local transfusion policy, whereas asymptomatic patients should be considered for intravenous iron.

Monitoring outcome data

Data from patients in Cardiff treated in the preoperative setting with intravenous iron who achieved Hb >130 g/l at the time of surgery showed a mean increase of 16.9 g/l (6-44 g/l IQR). These patients had lower serum ferritin and CRP at presentation. The group that had an increased haemoglobin with IV iron but did not reach Hb 130g/l at the time of surgery, had a lower Hb at presentation, higher ferritins and higher creatinine suggestive of a mixed iron deficiency picture.

Treating anaemia with intravenous iron in the preoperative setting has limited randomised controlled trial evidence. The results of the PREVENTT study - intravenous iron versus placebo in major non cardiac surgery [30] do not show a statistical difference in packed red cell use but do demonstrate an increase in haemoglobin and improvement in functional status. The authors acknowledge the criteria for inclusion did not assess the iron status of patients preoperatively, only the haemoglobin. The dosing of intravenous iron and time to surgery, which were too low and too short in this study are other contributary factors as to why this study does not demonstrate significant results.

Our own experience gives us the view that haemoglobin and transfusion are poor measurements of patient outcome. The integral role that iron has at a cellular level means the outcome measures used in this study were not subtle enough to show the true benefits of iron treatment. Further work on the benefits of perioperative iron are essential to unravel the complex mechanisms and cellular benefits that iron treatment affords. In the meantime a wealth of expert guidance on identification and management exist to adapt and apply in your own perioperative care setting [31,32].
References

5. NICE Blood Transfusion. NICE Guideline NG24 2015 nice.org.uk/guidance/ng24 (accessed 01/07/2020)
Figure 1: Pre-operative anaemia pathway

Pre-op bloods
- FBC
- Ferritin
- Transferrin Saturation (TSAT)
- Anaemia screen*
- U&E
- CRP
- G&S

Is the patient anaemic?
Hb <130g/L (male and female)

Yes
- Major Surgery?
  - Any of:
    - Estimated blood loss >500ml
    - Transfusion risk >10%
    - G&S required
  - Intermediate/low risk surgery
    - Standard pre-op surgery if indicated: FBC, anaemia screen*, U&E

No
- Intermediate/low risk surgery
  - Standard pre-op surgery if indicated: FBC, anaemia screen*, U&E
  - If anaemia found, consider cause, treatment and refer as appropriate.

No anaemia: Ferritin <100 mcg/L
- Consider iron therapy if anticipated post-op Hb decrease is ≥30g/L
- Consider cause and need for GI investigations if ferritin <30 mcg/L (note 1)

Iron deficiency anaemia
- Assess cause (note 1)
  - Surgery within 6 weeks
    - IV iron therapy
  - >6 weeks until surgery
    - Start oral iron (ferrous fumarate 210mg OD)
    - Prescription posted to patient with lab form for repeat FBC in 6 weeks
    - Patient logged onto POAC database for follow-up up in 6 weeks
    - If Hb improves proceed to surgery
    - If poor response, consider IV iron

Ferritin < 30 mcg/L

Ferritin 30-100 mcg/L
+ TSAT < 20%
or CRP >5 mg/L

Anaemia of chronic inflammation with iron deficiency
- IV iron therapy
- Consider cause and refer as appropriate (note 2)

Ferritin 30-100 mcg/L
+ TSAT > 20%
and CRP < 5 mg/L

Possible anaemia of chronic inflammation or other cause
- Check B12, Folate, Creatinine
- Consider IV iron therapy
- Consider cause and refer as appropriate (note 2)

Ferritin >100 mcg/L
+ TSAT < 20%
or CRP >5 mg/L

Anaemia of chronic inflammation
- Consider IV iron therapy
- Consider cause, check B12 and folate and refer as appropriate (note 2)

Ferritin >100 mcg/L
+ TSAT > 20%
or CRP <5 mg/L

Other causes - Chronic kidney disease, B12/Folate deficiency
- Check B12, Folate, Creatinine
- Refer to nephrologist if kidney disease

Footnotes
* Anaemia screen performed by lab if Hb <130g/L + ferritin, B12, folate.
* Note 1: Assess source of blood loss and refer as appropriate or refer to GI if no obvious source and either adult male, postmenopausal female, or premenopausal female with GI symptoms. Patients without a clear physiological explanation for iron deficiency (especially men and postmenopausal women) should be evaluated by gastroscopy/colonoscopy to exclude a source of GI bleeding, particularly a malignant lesion. Determine possible causes based on history and examination; initiate iron therapy; screen for coeliac disease; discuss timing of scopes with a gastroenterologist.
* Note 2: Possible causes: inflammation, malignancy, infection, liver disease, renal failure, thalassaemia trait, sideroblastic anaemia. Check Creatinine, LFTs, TTF, B12, Folate.
Figure 2: The Cardiff prescription, pre infusion questionnaire and patient monitoring proforma

**Prescription Chart for Monofer (iron(III) isomaltoside 1000) in Cardiac Surgery**

**Allergies**
- Please circle as appropriate
- NONE KNOWN
- YES

**Signature**
- Name: ____________________________
- Drug/allergen: __________________
- Description of reaction

**Prescriber to complete all boxes shaded in grey**
Monofer to be prescribed if haemoglobin < 130 g/L and ferritin <100 mcg/L.
In patients having complex valve/aortic surgery or a redo procedure, Monofer to be prescribed in all patients with a ferritin <100 mcg/L (even if Hb greater 130g/L) – see Preoperative Anaemia Pathway.

**Step 1 Justify need for parenteral iron therapy**

<table>
<thead>
<tr>
<th>Hb (&lt;130 g/L)</th>
<th>Ferritin (&lt;100mcg/L)</th>
<th>Planned surgery</th>
<th>Weight (kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Complex valve/aortic</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Redo valve/graft</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Other (specify indication)</td>
<td></td>
</tr>
</tbody>
</table>

**Step 2 Dose = 20mg/kg – tick dose as appropriate (calculate if weight <50kg)**

<table>
<thead>
<tr>
<th>Weight &lt;50 kg</th>
<th>50-59 kg</th>
<th>60-69 kg</th>
<th>70-79 kg</th>
<th>80-89 kg</th>
<th>90-99kg</th>
<th>≥ 100kg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dose 20mg/kg</td>
<td>1g</td>
<td>1.2g</td>
<td>1.4g</td>
<td>1.6g</td>
<td>1.8g</td>
<td>2g</td>
</tr>
</tbody>
</table>

**Step 3 Complete the Monofer Prescription Schedule**

<table>
<thead>
<tr>
<th>DATE</th>
<th>Drug name and infusion</th>
<th>DOSE</th>
<th>ROUTE</th>
<th>Prescriber signature</th>
<th>TIME GIVEN</th>
<th>GIVEN BY</th>
<th>CHECKED BY</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Sodium Chloride 0.9% for flushing cannula</td>
<td>5ml</td>
<td>IV</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Iron (III) Isomaltoside (Monofer*) in 500ml Sodium Chloride 0.9% over 60 minutes</td>
<td>IV infusion</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Sodium Chloride 0.9% for flushing cannula</td>
<td>5ml</td>
<td>IV</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Step 4 Prescriber’s signature**

<table>
<thead>
<tr>
<th>PRINT name</th>
<th>Designation</th>
<th>Signature</th>
<th>Date</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

**Step 5 Clinical Check by Pharmacist, dispensing and accuracy check**

<table>
<thead>
<tr>
<th>Clinical check</th>
<th>Dispensing</th>
<th>Final check</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

PTO
Pre-administration questionnaire and monitoring

<table>
<thead>
<tr>
<th>Past medical history</th>
<th>Liver disease</th>
<th>Rheumatoid arthritis/SLE</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>asthma</td>
<td>Previous sensitivity to iron</td>
</tr>
<tr>
<td></td>
<td>eczema</td>
<td>Other drug allergies</td>
</tr>
</tbody>
</table>

If any of the above apply, the patient will be at a greater risk of hypersensitivity reactions. Please be aware that the infusion may need to be slowed down or stopped (see Reaction Management Algorithm).

**Monitoring**

<table>
<thead>
<tr>
<th></th>
<th>Time</th>
<th>Temperature</th>
<th>Respiratory rate</th>
<th>Blood pressure</th>
<th>Pulse</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before Infusion</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>After 30 minutes</td>
<td></td>
<td>n/a</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>After 60 minutes</td>
<td></td>
<td>n/a</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>30 minutes after completion of infusion</td>
<td></td>
<td>n/a</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Anaphylaxis**

Acute severe anaphylactic reactions may occur with parenteral iron administration. They usually occur within the first few minutes of administration and are characterised by sudden onset respiratory failure and/or cardiovascular collapse. Urticaria, rashes, itching, nausea and shivering may also occur. Administration must be stopped immediately if signs of an anaphylactic reaction are observed. Appropriate resuscitation medication must be available including hydrocortisone IV and adrenaline. See Reaction Management Algorithm.